

We claim:

1. A method for determining the nuclear packing efficiency (NPE) of a cell, comprising the steps of
 - 5 (a) measuring a biochemical component (BC) of the nucleus of a cell;
 - (b) measuring a spatial displacement of the nucleus (SDN) of the cell; and
 - 10 (c) determining a nuclear packing efficiency (NPE) by correlating the values of BC and SDN.
2. The method of claim 1, wherein the SDN is the volume of a particle selected from the group consisting of a procaryotic cell and a virus.
3. The method of claim 1, wherein the SDN is
15 the volume of a eucaryotic nucleus.
4. The method of claim 3, wherein the SDN is measured using electronic cell volume (ECV) to yield an electronic nuclear volume (ENV).
5. The method of claim 4, wherein the ENV is
20 adjusted using flow cytometry time-of-flight (TOF).
6. The method of claim 1, wherein the BC includes nucleic acid.
7. The method of claim 6, wherein the nucleic
25 acid is DNA.

8. The method of claim 7, wherein the DNA is measured by fluorescence.

9. The method of claim 6, wherein the nucleic acid is RNA.

5 10. The method of claim 1, wherein the BC includes nuclear envelope lipid.

11. The method of claim 1, wherein the BC includes nuclear protein.

10 12. The method of claim 11, wherein the nuclear protein is nuclear matrix proteins (NMP).

13. The method of claim 11, wherein the nuclear protein is histones.

14. The method of claim 11, wherein the nuclear protein is nuclear-envelope-associated proteins.

15 15. The method of claim 14, wherein the nuclear-envelope-associated protein is a nuclear pore protein.

16. The method of claim 1, wherein the BC includes nuclear water.

17. The method of claim 1, wherein step (c) is performed according to the formula

$$\text{NPE} = k_1(\text{BC})^a/(\text{SDN})^b + k_2(\text{BC})^c + k_3(\text{SDN})^d + k_4;$$

wherein k_1 , k_2 , k_3 , k_4 , a , b , c and d are preselected constants and k_1 is not zero.

18. The method of claim 17, wherein k_1 is positive.

19. The method of claim 17, wherein k_2 is zero.

20. The method of claim 17, wherein k_4 is zero.

21. The method of claim 17, wherein $k_1 = 1$, $a = 1$ and $b = 1$, whereby $\text{NPE} = \text{BC}/\text{SDN}$.

22. The method of claim 17, further comprising the step of measuring a second biochemical component (BC_2).

23. The method of claim 22, wherein BC_2 is selected from the group consisting of total nucleic acid, DNA, RNA, nuclear protein, nuclear matrix protein, histones, nuclear envelope lipid and nuclear-envelope-associated proteins.

24. The method of claim 22, wherein the amount of $k_5(\text{BC}_2)^e$ is added to the value of BC measured in step (a), wherein k_5 and e are preselected constants.

25. The method of claim 24, wherein BC_2 is DNA, $k_5 = 1$ and $e = 1$.

26. The method of claim 22, wherein the amount of $k_5(BC_2)^e$ is added to the value of SDN measured in step (b), wherein k_5 and e are preselected constants.

27. The method of claim 26, wherein BC_2 is RNA,
5 $k_5 = 1$ and $e = 1$.

28. The method of claim 22, wherein the NPE in step (c) is multiplied by $k_5(BC_2)^e$, wherein k_5 and e are preselected constants.

29. The method of claim 28, wherein BC_2 is
10 nuclear protein, $k_5 = 1$ and $e = 1$.

30. The method of claim 1, wherein step (c) is performed by performing the steps of

(c1) determining a datapoint for BC and SDN on separate axes for BC and SDN; and

15 (c2) determining NPE as the slope of a line passing through the datapoint and the origin of the axes.

31. A method for determining an NPE for a population of cells, comprising the steps of

5 (a) for a representative number of cells in the population:

- (1) measuring a biochemical component (BC) of the nucleus of a cell;
 - (2) measuring a spatial displacement of the nucleus (SDN) of the cell; and
 - 10 (3) determining a datapoint for BC and SDN on separate axes for BC and SDN;
- (b) identifying at least one cluster of the datapoints; and
- 15 (c) determining an NPE according to a preselected geometric parameter of the cluster of datapoints.

32. The method of claim 31, wherein the geometric parameter is the slope of a substantially linear curve passing through the local maxima of at least
20 one cluster and through the origin of the BC and SDN axes.

33. The method of claim 31, wherein the geometric parameter is the slope of the gradient line of the cluster of datapoints.

34. The method of claim 31, wherein the geometric parameter is selected from the group consisting of eccentricity, maximum range of the major axis, maximum range of the minor axis, standard deviation of the major axis, standard deviation of the minor axis, slope of a line orthogonal to the gradient line, and perimeter.

35. A method for identifying different cells within a population of cells, comprising the steps of

10 (a) performing the method of claim 1 on at least one cell in the population; and

(b) identifying the cell if the cell's NPE is within at least one predetermined NPE range.

36. The method of claim 35, further comprising the step of

15 (c) segregating the identified cell from non-identified cells.

37. A method for identifying a cell, having a phenotype of interest, that is present in a population of cells, comprising the steps of

20 (a) performing the method of claim 31 on a population of cells to determine an NPE from at least one cluster of datapoints; and

(b) determining whether the NPE is within a predefined range for the geometric parameter.

38. The method of claim 37, wherein the predefined range is within a range of BC and within a range of SDN.

39. The method of claim 37, wherein the
5 phenotype is being of a different sex.

40. The method of claim 37, wherein the phenotype is being of a different tissue.

41. The method of claim 37, wherein the phenotype is being of a different species.

10 42. The method of claim 37, wherein the phenotype is being of a different state of differentiation.

43. The method of claim 42, wherein the geometric parameter is increased major axis.

15 44. The method of claim 37, wherein the phenotype is being at a preselected cell division cycle stage.

45. The method of claim 44, wherein one stage cycle is S.

20 46. The method of claim 45, wherein the geometric parameter is increased major axis.

47. The method of claim 44, wherein a stage cycle is selected from the group consisting of G_0 , G_1 , G_2 and M.

48. The method of claim 37, wherein the phenotype is being in an apoptotic state.

49. The method of claim 37, wherein the phenotype is being of a disease state.

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50. The method of claim 49, wherein the disease state is a genetic disease.

51. The method of claim 50, wherein the disease state is sickle cell anemia.

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52. The method of claim 50, wherein the disease state is Down's syndrome.

53. The method of claim 49, wherein the disease state is an autoimmune disease.

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54. The method of claim 37, wherein the phenotype is aneuploidy.

55. The method of claim 37, wherein the phenotype is being neoplastic.

56. The method of claim 55, wherein the geometric parameter is increased major axis.

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57. The method of claim 55, wherein the indication of a different cell type is indicative of a malignant cell.

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58. The method of claim 57, wherein the geometric parameter is reduced slope of the gradient line.

59. The method of claim 55, wherein the indication of a different cell type is indicative of a metastasizing cell.

60. The method of claim 59, wherein the geometric parameter is broadened minor axis.

61. The method of claim 54, wherein the cell is from breast tissue.

62. The method of claim 54, wherein the cell is from cervical tissue.

63. The method of claim 54, wherein the cell is from lung tissue.

64. The method of claim 54, wherein the cell is from tissue selected from the group consisting of colon, gastric, lymphatic, intestine and prostate.

65. The method of claim 54, wherein the cell is from tissue selected from the group consisting of brain, ovary, testes, bone and exfoliated circulatory tissue.

66. A device for determining the NPE of a cell, comprising

a first means for measuring a biochemical component of a nucleus from at least one cell (BC);

- 5 a second means for measuring the spatial displacement (SDN) of the nucleus of at least one cell; and

means for determining a nuclear packing efficiency (NPE) by correlating the values of BC and SDN.